UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

IN RE: BENICAR (OLMESARTAN) PRODUCTS LIABILITY LITIGATION	**MDL No. 2606**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 15-2606 (RBK)(JS)**

PLAINTIFFS' BRIEF IN OPPOSITION TO DEFENDANTS' MOTION TO EXCLUDE THE GENERAL CAUSATION TESTIMONY OF PLAINTIFFS' EXPERT STEPHEN LAGANA, M.D.

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PRELIMINARY STATEMENT

Defendants challenge Dr. Stephen Lagana's methodology only. On close inspection, the motion is primarily focused on Dr. Lagana's conclusions, failing to establish any legitimate flaw in his methodology. The motion is falsely premised on mischaracterizations of Dr. Lagana's opinions, including partial citations and out of context attacks on answers and lines of testimony. In essence, the defense previews a cross-examination that would go to the weight of the conclusions reached at most, but in no way would establish that Dr. Lagana failed to apply an acceptable scientific approach in order to reach his opinions. In fact, Dr. Lagana testified to applying the very methodology that the defense brief agrees is reliable, the Bradford Hill criteria.

Dr. Lagana is a pathologist at Columbia University, with a focus on gastrointestinal pathology. He works closely with the Columbia University Celiac Center, and in that capacity was made aware of Olmesartan induced enteropathy ("OIE") months before the publication of the Rubio-Tapia publication by Mayo Clinic physicians which first explicitly discussed this entity in the literature. Dr. Lagana has direct clinical experience in the diagnosis and treatment of OIE, through the interpretation of histopathological biopsy specimens and interaction with the gastroenterologists treating these patients. He has also co-authored peer reviewed publications on OIE, and in that capacity has studied and relied on the medical literature, in addition to his own contributions to this body of scientific knowledge. Unlike the defense experts, Dr. Lagana was immersed in and knowledgeable about this condition for years before he was contacted to be an expert in this litigation, and applied the very opinions and methods he has utilized in his clinical and research activities. Dr. Lagana's methodology is sound, and the motion should be denied.

STATEMENT OF FACTS

Dr. Stephen Lagana is a fellowship trained pathologist employed at Columbia University. He has extensive experience in the evaluation of small intestinal biopsies, including cases of suspected or confirmed celiac disease, and the condition at issue in this litigation, Olmesartan induced enteropathy ("OIE"). (See: Dr. Lagana's report and CV; Slater Cert., Exhibit 1). His knowledge of and interest in OIE dates back to early 2012, when he learned through the senior clinician of the Columbia Celiac Center, Dr. Peter Green, that Dr. Joseph Murray, the senior author on the Mayo Clinic study that would come to be known as the Rubio Tapia study, would be published in a few months. Rubio-Tapia, MD., Herman, MD., Ludvigsson, MD, PhD, Kelly, PhD, Mangan, MD, Wu, MD, PhD, Murray, MD. *Severe Spruelike Enteropathy Associated with Olmesartan*. Mayo Clin Proc., August 2012;87(8):732-738. *prevalence of celiac disease in the United States.* Am J Gastroenterol. 2012 Oct;107(10):1538-44. (Slater Cert., Exhibit 2). From that point forward, Dr. Lagana became very interested in this clinical entity, has closely followed the literature, and has published articles discussing OIE. (Dr. Lagana Dep. Tr., 26:18-27:16; Slater Cert. Exhibit 3). For example, in one article he and his co-authors performed a systematic review of the relevant literature, including numerous studies and case reports, all leading to the accepted conclusion that Olmesartan causes sprue-like enteropathy. For example, the Summary at the beginning of the article refers to "This syndrome" as an "adverse drug reaction," refers to, "histopathologic distinction of olmesartan-associated enteropathy from other causes of sprue (eg, celiac disease, tropical sprue)," and finally, "Lastly, we will discuss the histopathologic differential diagnosis and provide clues to distinguish this entity from other entities which can cause sprue-like histopathology." Burbure N, Lebwohl B, Arguelles-Grande C, Green PH, Ghagat G, and Lagana SM. *Olmesartan-associated sprue-like enteropathy: a systematic review with emphasis on*

histopathology. Human Pathology (2016) 50, 127-134. (Slater Cert., Exhibit 4). Dr. Lagana confirmed in his deposition that his opinion on general causation was formed in the context of his clinical practice, and the research and publications he has been involved in, long before he was ever contacted and asked to serve as an expert in this litigation. (Dr. Lagana Dep. Tr.,24:16-27:16).

Defendants' motion is premised on mischaracterizations of Dr. Lagana's opinions and testimony, starting with their argument that he does not define the condition with adequate specificity. For example, the defense claims that Dr. Lagana testified that, "There is no cardinal finding that can establish the diagnosis," citing the deposition transcript at 232:11-17. (Defense brief at 2). In fact, the cited testimony is part of a discussion about the Burbure et al. article cited above, in the context of differentiating OIE and, "other entities which may histologically resemble olmesartan enteropathy," such as celiac disease, and mycophenolate. The testimony cited by the defense is extremely misleading as it leaves out a key part of what Dr. Lagana actually testified to. Dr. Lagana actually stated, quoting the article, "there is no cardinal finding which can establish the diagnosis of olmesartan-induced injury **based solely on histopathology**." (Dr. Lagana Dep. Tr., 218:14-232:17), emphasis added. Burbure, et al. at 132. This is simply a recognition that the histopathology demonstrated on pathology specimens is similar across these entities, thus the clinical context is an important part of differentiating in an individual patient.

The defense inexplicably criticizes Dr. Lagana for expressing the peer reviewed scientific fact that OIE is a, "clinicopathologic diagnosis," (Dr. Lagana Dep. Tr., 59:13-60:9). In fact, on page 5 of his report, Dr. Lagana quotes the seminal Rubio-Tapia article: "Pathologic findings in the duodenal biopsy can mimic celiac disease or collagenous sprue. Clinicopathologic correlation is advised to confirm the diagnosis of olmesartan-associated enteropathy." (Dr. Lagana report, p.5; Slater Cert., Exhibit 1). (See: Rubio-Tapia, et al., at 735; Slater Cert., Exhibit 2). Dr. Lagana

echoed this in one of his own articles: "Although we have attempted to provide histopathologic features which may aid in the differential diagnosis, definitive diagnosis requires clinicopathological correlation, highlighting the importance of effective 2-way communication between pathologists and gastroenterologists." Burbure, et al., at 133. (Slater Cert., Exhibit 4).

The defense adds another related criticism based on yet another misrepresentation, claiming that Dr. Lagana "skirted specifics," in describing pathologic criteria. (Defense brief at 2-3). In fact, Dr. Lagana provided a very detailed discussion of the pathologic features seen with OIE:

> A. Olmesartan enteropathy affects the entire gastrointestinal tract as far as we know, most prominently in the small intestine, but also prominently in the stomach and the colon. And the way that we can identify that injury histologically, the most common finding, although it's not the only finding, is inflammation and that inflammation may be lymphocytic or plasmacytic -- these are different types of inflammatory cells -- and often those are the cells that are referred to as chronic inflammatory cells, and we also find acute inflammatory cells such as neutrophils. Those cells can be distributed variably throughout -- throughout the gut and even in a certain tissue location. You might find the lymphocytes in the lamina propria. You might find them in the epithelium, so-called intraepithelial lymphocytosis, and the same can be said of the neutrophils, eosinophils, et cetera. And what we see as sequelae of this inflammation, we see a variable picture. The most extreme example in the duodenum or in the small intestine would be flattening of the duodenal villi -- or, actually, I should say all the small intestinal villi – as well as potentially fibrosis of the lamina propria. The inflammation and the fibrosis can also be seen in the stomach and the colon. There's no potential for villous atrophy in the stomach or colon because there are no villi in either the stomach or the colon. And so, you know, these are a -- what I have described for you now are examples of what we can see. It's not everything that we can see and, in some cases, it's the most extreme example.
>
> Q. And I don't want to cut you off. I want to make sure you -- before I follow up with you. Are you done with your

answer?

A. There are additional histologic findings that I've noticed. Some patients have markedly increased crypt apoptosis, which is death of cells in a part of the tissue where they should be proliferating, not dying. I've encountered recently a case of granulomatis inflammation associated with olmesartan enteropathy, which was new to me. I've seen crypt atrophy which resembles autoimmune enteropathy where you see a loss of the crypts. I've also seen crypt architectural distortion, such as branched crypts, which is typically seen in inflammatory bowel disease. So I would say that there's a pretty wide range of presentations pathologically and really one needs to be aware that it exists to make the diagnosis.

(Dr. Lagana Dep. Tr., 60:17-64:1).

Defendants also inaccurately claim that Dr. Lagana opined that any gastrointestinal problem that improves when Olmesartan is withdrawn falls within the diagnosis, citing 73:3-77:19. (Defense brief at 2). Dr. Lagana actually testified that the entire clinical picture must be considered, and that depending on the presentation there would be weaker and stronger cases, with a positive dechallenge clearly standing as an important piece of evidence to be weighed. Contrary to the defense's mischaracterization, he actually **ruled out** a hypothetical presented by defense counsel: "if someone had minimal abdominal pain for three – you know, for a few days and stopped taking olmesartan and they improved, **I would not personally find that to be a very plausible case of sprue-like enteropathy**." (Dr. Lagana Dep. Tr., 71:16-78:15), emphasis added. Therefore, Dr. Lagana actually testified to the opposite of what the defense claims in their brief.

The defense also suggests that Dr. Lagana testified that one never needs to rule out other potential causes in order to establish the diagnosis of OIE, citing to an isolated question and answer at 177:16-20 (sic.). (Defense brief at 2). In fact, this testimony is found in the context of a long discussion about what happens in actual clinical practice, that began with analysis of a table listing

clinical features of OIE found in the initial Rubio-Tapia publication from the Mayo Clinic. Rubio Tapia, et al. at 737, citing Table 3, titled: "Clinical Features of Sprue-like Enteropathy Associated with Olmesartan." (Slater Cert., Exhibit 2). In that discussion, the questioning turned to whether there is an "absolute requirement," that a gastroenterologist rule out all other potential causes, "in clinical practice now," in the actual treatment of a patient – where there is demonstrated, "evidence of clinical improvement after suspension of olmesartan," which he termed, "the key feature." (Dr. Lagana Dep. Tr., 170:9-180:9). Dr. Lagana actually testified that if, "a gastroenterologist did nothing except stop Olmesartan," failing to take any steps to for example test for and rule out celiac disease, "they would have a decent chance of being wrong…they could miss a case of actual celiac disease, absolutely." Id. The defense's argument therefore conflates a discussion of the reasonableness of a clinician in actual practice forming a working diagnosis of OIE based on a positive dechallenge, with the establishment of a firm diagnosis based on consideration of broader clinical information such as celiac testing and clinical response to gluten. This discussion of what specialists are actually doing in clinical practice, in part to avoid ultimately unnecessary testing and invasive intestinal biopsies (175:12-176:14), actually demonstrates the overwhelming consensus establishing general causation in the minds of the specialists who are most knowledgeable about OIE.[1]

The defense's claim that Dr. Lagana did not consider the Bradford Hill criteria is specious. In his deposition, Dr. Lagana confirmed that when he wrote his report, he was, "aware of and understood the Bradford Hill factors criteria," and explained that in medical science, "They are a

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[1] Dr. Lagana's reasonable position that he would defer to a gastroenterologist as to what, "degree of clinical improvement would be needed before someone can conclude there's been successful dechallenge," in the context of a hypothetical discussion assuming no improvement on pathology, further demonstrates the reasonableness of his methodology. (Dr. Lagana Dep. Tr., 197:14-198:20).

set of questions which are used to address cause and effect." When asked to confirm that the criteria are not "mentioned" in his report, he answered, "Not specifically, no." He also confirmed that the criteria, "influences my thinking." (Dr. Lagana Dep. Tr., 356:8-357:24). Dr. Lagana confirmed that he took the Bradford Hill criteria into account in performing his analysis:

> Okay. I think that those factors are fundamental to how people in medicine think about medical science, and certainly I did think about them and I did address them, although not in the context of listing the criteria point -- on a point-by-point basis. But, yeah, I did think about them and I did try to incorporate them.

(Dr. Lagana Dep. Tr., 406:10-20). In this context, he confirmed his familiarity with the actual list of criteria, "Strength of association, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experimental evidence, and analogy." (Dr. Lagana Dep. Tr., 407:2-10). In very illustrative testimony of Dr. Lagana's application of the Bradford Hill criteria, he testified in detail regarding his application of the strength of association and consistency factors in evaluating and relying on the Basson study of the French epidemiologic database:

> Q. Now, looking at the Basson article -- I'm just going to turn to it real quick -- and looking at page 5 of the article, and there's a statement here on the top left, "The strength of the association and the consistency with reported cases (including the long lag time between initiation of olmesartan and diagnosis of malabsorption) are strong arguments in favor of causality." Is that statement of any significance to you?
>
> A. Well, yeah, I think it's a -- it's a strong statement. They're applying the Bradford Hill criteria there, or at least some of them, and I think that -- well, they've said it quite plainly, that their findings are strong evidence in favor of causality, and I agree with that.
>
> Q. You mentioned –
>
> A. And by the way, if I could just mention another thing about this study –

Q. Sure.

A. -- which I don't think that we got to too specifically, when you look at the strength of the association, the relative risk of 5 or 10 as is seen after two years of therapy on olmesartan, that's a very high relative risk.

Q. And why is that significant?

A. **Well, again, getting back to the -- if we think about the Bradford Hill criteria, the strength of the association, the fact that there's a tenfold increased risk is strong.**

(Dr. Lagana Dep. Tr., 403:17-405:5) emphasis added.

Finally, the suggestion that Dr. Lagana could not adequately define general causation is specious. Dr. Lagana clearly testified: "**So in the public at large, yes, I certainly believe olmesartan is causative of sprue-like enteropathy in some patients.**" (Dr. Lagana Dep. Tr., 24:3-6), emphasis added. He similarly testified that after initially learning of this disease: "I've followed the medical literature pretty closely. I read everything I see that relates to olmesartan enteropathy and I have over time certainly become more convinced that this drug does cause this syndrome in some patients." (Dr. Lagana Dep. Tr., 2:10-16). This is the definition of general causation.[2]

[2] Defendants' effort to make an issue of Dr. Lagana's responses to defense counsel's questioning as to the occurrence of OIE in the "general population," is disingenuous at best. Dr. Lagana clearly didn't want to suggest that OIE happens to the "general population." Drawing an analogy to celiac: "I wouldn't say gluten in a general population causes [celiac disease] because, you know, 98 or 99 percent of us eat gluten with no negative effects. (Dr. Lagana Dep. Tr., 21:7-22:8). This was nothing more than a semantic issue, and his testimony makes perfect sense.

LEGAL ARGUMENT

I.

DR. LAGANA'S METHODOLOGY IS RELIABLE

The admissibility of expert testimony is determined pursuant to Rule 702, which incorporates the Daubert standard.

> In determining reliability, a court may look to several non-exhaustive factors, including:
>
> (1) whether a method consists of a testable hypothesis; (2) whether the method has been subject to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put.

Geiss v. Target Corp., 2013 WL 4675377 at *4 (D.N.J. 2013) (quoting Elcock v. Kmart Corp., 233 F.3d 734, 745-47 (3d Cir. 2000)(Slater Cert., Exhibit 5). Application of these factors demonstrates that Dr. Lagana's opinions are absolutely admissible.

"Rule 702 has a liberal policy of admissibility." Geiss, 2013 WL 4675377 at *4 (citing Pineda v. Ford Motor Co., 520 F.3d 237, 243 (3d Cir. 2008), other citations omitted. The Third Circuit, "made clear in Paoli II, an expert's level of expertise may affect the reliability of the expert's opinion." Elcock, 233 F.3d 734, 746 (quoting In re Paoli R.R. Yard PCB Litigation, 35 F.3d 717, 741 (3d Cir. 1994) ("Paoli II")). Dr. Lagana's extensive qualifications, including publication of peer reviewed literature on this subject, should therefore bear upon the reliability inquiry. See Elcock, 233 F.3d at 746; Paoli II, 35 F.3d at 741.

Very recently, in the Xarelto litigation, a series of similar Daubert motions were summarily denied, with the Court succinctly opining that the plaintiffs' experts applied the proper methodology, and relied on peer reviewed literature, thus the balance of the defense's criticisms

went to the weight of the opinions, not admissibility. See In re Xarelto (Rivaroxaban) Prod. Liab. Litig., Case No. 2:14-MD-02592, Doc 6198, 2017 WL 1352860 (E.D.La, April 13, 2017). (Slater Cert., Exhibit 6). With particular relevance to this case, the Court noted that plaintiffs' gastroenterologist, Dr. Winstead, "attests that he used the same methods he uses to evaluate and treat his patients" in writing his expert report. Id., 2017 WL 1352860 at *5. "The Court finds Dr. Winstead is qualified by virtue of his training and experience. He reaches his conclusion that NOACs, and specifically Xarelto, can cause bleeding without underlying pathology through his experience, the presence of the drug in Plaintiff's stool, peer reviewed literature, and Xarelto's label. Defendants may cross-examine Dr. Winstead on these issues at trial." The same result is appropriate here.

Daubert requires that an expert, whether basing his opinions upon studies or personal experience, "employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." Elcock, 233 F.3d at 746 (3d Cir. 2000) (quoting Kumho Tire Co. v. Carmichael, 526 U.S. 137, 152 (1999)). Dr. Lagana applied the methods and knowledge he uses in his clinical and academic work at Columbia University, and offers an opinion that he has expressed in peer reviewed medical literature, clearly satisfying these standards.

The only question raised as to Dr. Lagana's methodology is whether he applied the Bradford Hill criteria. Dr. Lagana's deposition testimony clearly establishes that he did consider and apply those factors, for example, explaining in some detail the significance of the Basson study and specifically referencing two of the Bradford Hill factors, strength of association and consistency (Dr. Lagana Dep. Tr., 403:17-405:5). He also discussed other Bradford Hill criteria, without specifically referencing back to Bradford Hill, for example referencing biological gradient with regard to the correlation of injury with length of use (Dr. Lagana Dep. Tr., 404:14:405:5);

discussing biological plausibility in the context of his opinion that the mechanism is an immune-mediated inflammatory condition at great length (Dr. Lagana Dep. Tr., 236:23-241:18, 298:19-305:9); discussing temporality, consistency, and experiment/cessation with regard to the dechallenge and rechallenge data (Dr. Lagana Dep. Tr., 151:4-153:20) "One or more of the factors may be absent even where a causal relationship exists and…no factor is a sine qua non of causation." Glynn v. Merck Sharp & Dohme Corp., 2013 WL 1558690, at *3 (D.N.J. April 10, 2013)(citing Magistrini v. One Hour Martinizing Dry Cleaner, 180 F.Supp. 2d 584, 593 n. 9 (D.N.J. 2002))(Slater Cert., Exhibit 7). In Glynn, the motion to preclude plaintiffs' expert on general causation under Daubert was denied because, as here, the expert considered the Bradford Hill factors, and the criticisms went to the weight, not admissibility of the testimony, concluding, "Defendant is free to address these issues on cross-examination…" Id. at *4.

The same outcome is warranted here. Defendants acknowledge Dr. Lagana's testimony regarding his familiarity with the Bradford Hill factors, and that he considered and applied these factors, leaving the defense to argue that the failure to actually refer to Bradford Hill by name somehow precludes the opinion. "Bradford-Hill criteria are used to assess whether an established association between two variables actually reflects a causal relationship. Because these criteria are so well established in epidemiological research, it appears that the experts often consider these factors without citation to Bradford–Hill." In re Avandia Marketing, Sales Practices & Products Liab. Litigation, 2011 WL 13576 at *3 (E.D.Pa., Jan. 4, 2011)(Slater Cert., Exhibit 8). Indeed, the question is one of form over substance, and certainly not a basis to exclude the opinions, which are also stated by the expert in the peer reviewed literature.

The balance of the Defendants' arguments, primarily based on mischaracterizations of Dr. Lagana's deposition testimony, go only to the conclusions reached, and the weight to be given

those conclusions. This is not a permissible attack under Daubert. The focus of the reliability inquiry is on the expert's principles and methodology, not on his conclusions. Glynn at *2, citing Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 594-95 (1993).

CONCLUSION

For the foregoing reasons, Defendants' motion to preclude Dr. Lagana's opinions under Daubert should be denied. Dr. Lagana applied a valid methodology, relying primarily on peer reviewed literature that he has contributed to. Whatever criticisms the defense may have are directed to the weight to be accorded to the testimony, and Dr. Lagana's conclusions, which are fully consistent with the consensus in the peer reviewed literature, and can be explored on cross-examination at trial.

Respectfully,

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Dated: April 21, 2017